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Effectiveness of Acarbose, an Alpha-Glucosidase Inhibitor, in Uncontrolled Non-Obese Non-Insulin Dependent Diabetes

D. R. Buchanan[1], A. Collier[1], E. Rodrigues[1], A. M. Millar[2], R. S. Gray[1], and B. F. Clarke[1]

[1] Diabetic and Dietetic Department and
[2] Radiopharmacy, Royal Infirmary, Edinburgh, UK

Summary. The effect of acarbose, an alpha-glucosidase inhibitor, on glycaemic control, was compared with placebo in a double-blind, randomised, group comparison study during 16 weeks in 20 non-obese non-insulin dependent diabetic patients in whom sulphonylurea treatment had been withdrawn.

There was significant deterioration in glycaemic control as assessed by HbA_1 following withdrawal of the sulphonylurea. There was no significant improvement in HbA_1 between weeks 0 and 16 in either the acarbose (11.3% and 12.4% respectively) or the placebo group (10.6% and 12.2% respectively). In both the acarbose and placebo treated groups fasting glucose and insulin concentrations were unaltered.

This study also suggests that acarbose was not an effective substitute for sulphonylureas in non-obese Type 2 diabetes uncontrolled by diet alone.

Key words: acarbose, sulphonylureas; alpha-glucosidase inhibitor, non-insulin dependent diabetes mellitus

Acarbose, an intestinal alpha-glucosidase inhibitor, delays the digestion of sucrose and starch in animals and healthy human volunteers by a dose-dependent competitive inhibition of the intestinal disaccharidases [1, 2]. It has been shown to improve glycaemic control in both insulin dependent and non-insulin dependent diabetics [3-6].

The aim of this study was to evaluate the effects of acarbose on glycaemic control in moderately severe non-insulin dependent diabetics and to determine whether any subsequent improvement, compared with a placebo treated group, was due to improvement in pancreatic beta-cell function.

Subjects and Methods

Twenty-nine non-obese non-insulin dependent diabetics, treated with a low refined carbohydrate/high complex carbohydrate/low fat diet and a sulphonylurea (chlorpropamide, glipizide, or glibenclamide) which had been previously withdrawn, were entered into a double-blind, randomized comparison study. The patients were of either sex, aged between 40 and 60 years, had been diabetic from three months to 10 years, and had a body weight within the range of 90 to 114% ideal (Metropolitan Life Insurance Tables). Patients were excluded if they were pregnant, had previously received insulin or a biguanide, or were taking a drug with a known diabetogenic effect. All patients had the purpose of the study explained to them and their informed consent was obtained.

The subjects were studied as outpatients and attended at monthly intervals for a total of 24 weeks. The sulphonylurea was withdrawn and the patients were then maintained on diet alone for a run-in period of 8 weeks. No dietary modifications were introduced during the study. The patients were then randomized to acarbose and placebo treatment groups (week 0) with a treatment period of 16 weeks. The dosages of acarbose and corresponding placebo were increased during the study as follows: weeks 0-2 50 mg t.d.s.; weeks 3-8 100 mg t.d.s.; weeks 9-12 200 mg mane, 100 mg with lunch, and 100 mg with the evening meal; weeks 13-16 200 mg mane, 100 mg with lunch, and 200 mg with the evening meal. A questionnaire for gastro-intestinal and other adverse effects was completed at each visit. If adverse effects became intolerable the patients were instructed to reduce the dosage of acarbose to that which could be tolerated.

Glycosylated haemoglobin (HbA_1) and 24-h urine glucose excretion were estimated at each visit

Table 1. Clinical details (at Week −8) of patients who completed the trial (mean ± SD)

Groups	n	Age (y)	Duration of diabetes (months)	Body weight (% of ideal)	HbA_1 (%)
Acarbose-treated	6 M, 3 F	60.1 ± 6.8	44.9 ± 28.6	101 ± 6.2	10.4 ± 2.8
Placebo-treated	8 M, 3 F	57.6 ± 8.2	50.6 ± 30.1	97.4 ± 10.7	8.8 ± 1.8

Table 2. Metabolic control (mean ± SD) at weeks 0 and 16 in the acarbose and placebo groups (NS not significant)

	Week 0			Week 16		
	Acarbose group ($n=9$)	Placebo group ($n=11$)		Acarbose group ($n=9$)	Placebo group ($n=11$)	
Weight (kg)	73.4 ± 9.3	69.5 ± 9.9	NS	70.2 ± 8.6	67.2 ± 9.8	NS
Fasting plasma glucose ($mmol \cdot l^{-1}$)	10.5 ± 3.3	11.6 ± 3.9	NS	11.4 ± 3.7	10.9 ± 5.0	NS
HbA_1 (%)	11.3 ± 2.7	10.6 ± 2.8	NS	12.4 ± 3.6	12.2 ± 4.0	NS
24-h Urinary glucose excretion ($mmol \cdot 24\ h^{-1}$)	142 ± 137.3	164 ± 124.2	NS	129.6 ± 133.9	134.6 ± 152.0	NS
Triglycerides ($mmol \cdot l^{-1}$)	1.5 ± 0.6	1.9 ± 1.8	NS	1.7 ± 0.5	1.7 ± 1.9	NS
Total cholesterol ($mmol \cdot l^{-1}$)	7.3 ± 1.1	6.6 ± 1.4	NS	7.2 ± 1.1	6.8 ± 1.8	NS
24-h Urinary C-peptide excretion ($nmol \cdot 24\ h^{-1}$)	16.8 ± 11.2	11.8 ± 9.2	NS	34.4 ± 22.8	28.4 ± 39.7	NS
Fasting plasma lactate ($mmol \cdot l^{-1}$)	1.1 ± 0.5	1.35 ± 0.4	NS	1.8 ± 0.9	1.31 ± 0.5	NS

throughout the study. At the beginning (Week 0) and end (Week 16) of the treatment period measurements were made of fasting plasma lipids, lactate, fasting plasma glucose, and 24-h urinary C-peptide to assess residual pancreatic beta cell function. Plasma glucose was measured by a Yellow Springs Glucose Oxidase analyser. HbA_1 was measured using commercially available agar plates, the normal range being 6–8% [7]. Urinary C-peptide was determined by radioimmunoassay [8]. Plasma cholesterol and triglyceride were determined using standard laboratory procedures.

Statistical analysis was by Student's paired and unpaired *t*-tests where appropriate. Values of $p < 0.05$ were considered significant.

Results

Nine subjects failed to complete the protocol, seven because of other commitments, one for non-adherence to the protocol, and one because of a prolapsed intervertebral disc. Of the twenty patients who completed the study nine received acarbose and eleven placebo. The two groups were comparable in respect of age, sex, duration of diabetes, percentage ideal body weight, and glycaemic control at the onset of the study (Week −8) (Table 1). After withdrawal of the sulphonylurea there was a deterioration in glycaemic control in both groups between Week −8 and Week 0, when they entered the randomized treatment group.

Table 3. Comparison of metabolic control (mean ± SD) in nine patients during treatment on sulphonylurea (Weeks −8) and on acarbose alone for 16 weeks (NS not significant)

	Sulphonylurea treatment	Acarbose treatment	
Random plasma glucose ($mmol \cdot l^{-1}$)	7.9 ± 3.2	12.0 ± 6.7	$p < 0.02$
HbA_1 (%)	10.5 ± 2.8	12.4 ± 3.4	$p < 0.01$
Weight (kg)	73.4 ± 9.3	70.2 ± 8.6	NS

There was no statistically significant difference between the two groups at 16 weeks in respect of fasting plasma glucose, HbA_1, 24-hour urinary glucose excretion, plasma triglyceride, plasma cholesterol, 24-h urinary C-peptide, and fasting lactate concentrations (Table 2).

It was noted that in the patients treated with acarbose, glycaemic control, assessed in terms of random plasma glucose, HbA_1, and weight, was considerably less effective than with previous treatment with a sulphonylurea (Table 3). While none of the patients on placebo experienced gastrointestinal adverse effects, six patients on acarbose experienced either diarrhoea or softer stools and four patients had minor symptoms of flatulence.

Discussion

Acarbose (Bayer) is an alpha-glucosidase inhibitor which diminishes carbohydrate digestion, resulting in its delayed absorption from the gut and reduced post-prandial rises in plasma glucose and insulin [1, 2]. In insulin dependent diabetes the addition of acarbose to each meal decreases post-prandial glucose peaks, mean blood glucose concentrations, and the amplitude of glycaemic excursions during the day [4, 9]. When given at night it has similar actions and also reduces the frequency of nocturnal hypoglycaemia [10]. In obese non-insulin dependent diabetics acarbose likewise reduces both plasma glucose excursions after meals and mean daily blood glucose concentrations [11]. In a double-blind comparison with metformin in obese non-insulin dependent diabetic patients acarbose was significantly more effective in reducing post-prandial hyperglycaemia, although the two drugs were comparable in regard to other measures of blood glucose control [12].

The adverse effects of flatulence and diarrhoea with acarbose are due to bacterial gas products from non-absorbed carbohydrate in the colon [13]. These symptoms became more marked at the higher doses used in the later weeks of the study, but did not merit withdrawal of patients from the trial.

The present study was designed to establish whether treatment with acarbose reduced hyperglycaemia in non-obese uncontrolled non-insulin dependent diabetics in whom sulphonylureas had been previously withdrawn, and also whether this was associated with alteration in insulin concentrations. Our data demonstrated that in these patients acarbose treatment after 16 weeks produced a slightly slower but not statistically different deterioration in mean plasma glucose. Presumably as a result of the poor improvement of glycaemic control on acarbose, no difference was demonstrated in insulin concentrations. These same patients had previously been acceptably controlled on a sulphonylurea, and this group of oral agents should remain the first line of choice in the management of uncontrolled non-obese non-insulin dependent diabetics.

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Dr. A. Collier
Diabetic and Dietetic Department
Royal Infirmary of Edinburgh
Lauriston Place
Edinburgh EH3 9YW, UK